PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 209/14, A61K 31/40, 31/405, C07D 209/26 — A1

(11) International Publication Number: WO 96/25397

(43) International Publication Date: 22 August 1996 (22.08.96)

(21) International Application Number: PCT/CA96/00080

(22) International Filing Date: 8 February 1996 (08.02.96)

(30) Priority Data:
388,929 15 February 1995 (15.02.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 388,929 (CON)
Filed on 15 February 1995 (15.02.95)

(71) Applicant *(for all designated States except US)*: MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GALLANT, Michel [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). GAREAU, Yves [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). GUAY, Daniel [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). LABELLE, Marc [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA). PRASIT, Petpiboon [CA/CA]; 16711 Trans Canada Highway, Kirkland, Quebec H9H 3L1 (CA).

(74) Agent: MURPHY, Kevin, P.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College, Montreal, Quebec H3A 2Y3 (CA).

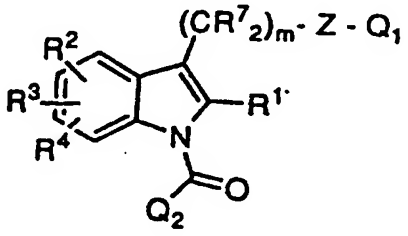
(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: INDOLE DERIVATIVES WITH AFFINITY FOR THE CANNABINOID RECEPTOR

(57) Abstract

Disclosed are indole derivatives of formula (I) having activity on the cannabinoid receptors and the methods of their preparation. The compounds are useful for lowering ocular intraocular pressure and treating glaucoma because of the activity of the cannabinoid receptor.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

TITLE OF THE INVENTION

INDOLE DERIVATIVES WITH AFFINITY FOR THE CANNABINOID RECEPTOR

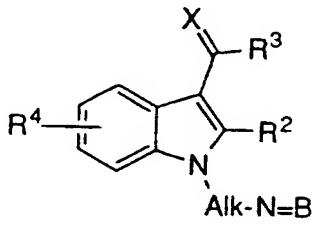
BACKGROUND OF THE INVENTION

The terms cannabinoid or cannabimimetic compound apply to compounds which produce a physiological effect similar to that of the plant Cannabis Sativa, or a compound that has affinity for the cannabinoid receptors CB_1 or CB_2. See Matsuda, L.; Lolait, S.J.; Brownstein,M.J.; Young, A.C.; Bonner, T.I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*, **1990**, *346*, 561-564: Munro, S.; Thomas, K.L.; Abu-Shaar, M. Molecular characterization of the peripheral receptor of cannabinoids. *Nature*, **1993**, *1993*, 61-65. Examples of such compounds are Δ^9-THC and its analogs (Razdan, R.K. Structure activity relationship in the cannabinoids. *Pharmacol. Rev.*, **1986**, *38*, 75-149), WIN-55212-2 and its analogs (D'Ambra, T.E.; Estep, K.G.; Bell, M.R.; Eissenstat, M.A.; Josef, K.A.; Ward, S.J.; Haycock, D.A.; Baizman, E.R.; Casiano, F.M.; Beglin, N.C.; Chippari, S.M.; Grego, J.D.; Kullnig, R.K.; Daley, G.T. Conformationnaly restrained analogues of Pravadoline: Nanomolar potent, enantioselective, aminoalkylindole agonist of the cannabinoid receptor. *J. Med. Chem.*, **1992**, *35*, 124-135: Bell, M.R.; D'Ambra, T.E.; Kumar, V.; Eissenstat, M.A.; Hermann, J.L.; Wetzel, J.R.; Rosi, D.; Philion, R.E.; Daum, S.J.; Hlasta, D.J.; Kullnig, R.K.; Ackerman, J.H.; Haubrich, D.R.; Luttinger, D.A.; Baizman, E.R.; Miller, M.S.; Ward, S.J. Antinociceptive aminoalkylindoles. *J. Med. Chem.*, **1991**, *34*, 1099-1100), CP-55940 and its analogs (Johnson, M.R.; Melvin, L.S. The discovery of non-classical cannabinoid analgetics. In "Cannabinoids as therapeutic agents", **1986**, Mechoulam, R., Ed., CRC Press: Boca Raton FL, pp.121-145), SR141716A and its analogs (Barth, F.; Casellas, P.; Congy, C.; Martinez, S.; Rinaldi, M. Nouveaux derives du pyrazole, procede pour leur preparation et composition pharmaceutiques les contenant. French Patent 2692575-A1, **1992**: Barth, F.; Heaulme, M.; Shire, D.; Calandra, B.; Congy, C.; Martinez, S.; Maruani, J.; Neliat,

G.; Caput. D.; Ferrara, P.; Soubrie, P.; Breliere, J-C.; Le Fur, G.; Rinaldi-Carmona, M. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. International Cannabis Research Society Conference Abstract, **July 1994**, L'EstÈrel, Canada, p. 33), and anandamide (Devane, W.A.; Hanus, L.; Breuer, A.; Pertwee, R.G.; Stevenson, L.A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, **1992**, *258*, 1946-1949) and its analogs. Anandamide has been termed the endogenous ligand of the CB_1 receptor, as it is synthesized near its site of action and is potent and selective for the CB_1 receptor.

The biological activity of cannabinoids has been extensively reviewed. See Hollister, L.E. Health aspects of Cannabis. *Pharmacol. Rev.*, **1986**, *38*, 1-20. Their usefulness in various disease states has been discussed. See The therapeutic potential of marihuana. Cohen, S. and Stillman, R.C., eds. Plenum: New York, **1976**.

Additionally, US patents 4,973,587 and 5,013,837 (Ward et al.) disclose compounds of formula 1:



1

having antiglaucoma compositions where:

R_2 is hydrogen, lower alkyl, chloro or fluoro;

R_3 is phenyl (or phenyl substituted by from one to three substituents selected from halogen, lower alkoxy, lower alkoxymethyl, hydroxy, lower alkyl, amino, lower alkylamino, di-lower alkylamino or lower alkylmercapto), methylenedioxyphenyl, benzyl, styryl, lower alkoxystyryl,

1- or 2-naphthyl,) or 1- or 2-naphthyl substituted by from one to two substituents selected from lower alkyl, lower alkoxy, halo or cyano), (1H-imidazol-1-yl)naphthyl, 2-(1-naphthyl)ethenyl,1-(1,2,3,4-tetrahydronaphthyl), anthryl, phenanthryl, pyrenyl,2-, 3-, 4-, 5-, 6- or 7-benzo[b]furyl, 2or 3-benzo[b]thienyl, 5-(1H- benzimidazolyl) or 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl;

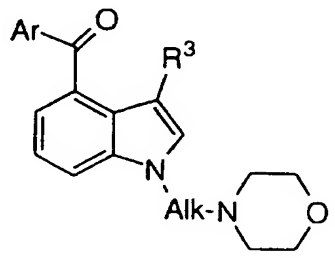
R_4 is hydrogen or lower alkyl, hydroxy, lower alkoxy or halo in the 4-, 5-, 6- or 7-positions;

X is O or S;

Alk is lower alkylene having the formula $(CH_2)_n$ where n is the integrer 2 or 3, or such lower-alkylene substituted by a lower-alkyl group; and

N=B is N,N-di-lower alkylamino, 4-morpholinyl, 2-lower alkyl-4-morpholinyl, 3-lower alkylmorpholinyl, 1-pyrrolidinyl, 1-piperidinyl or 3-hydroxy-1-piperidinyl.

US patent 5,081,122 (Ward) discloses compounds of formula 2:

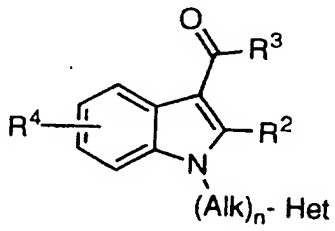


2

having antiglaucoma compositions where:
Ar is lower alkoxyphenyl or 1- or 2-naphthyl;
R_3 is hydrogen or lower alkyl;
Alk is lower alkylene containing from two to four carbon atoms.

The present compounds differ from Ward's (formula 1 and 2) primarily in having a carbonyl on the nitrogen of the indole while it is at the 4-position in the case of the US patent 5,081,122.

EP 0 444 451 generically discloses a compound of formula 3:



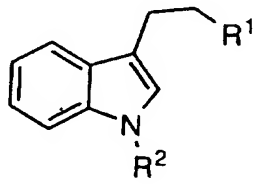
3

useful as analgesic, anti-rheumatic, anti-inflammatory or anti-glaucoma agents where:

R_2	is hydrogen, lower alkyl;
R_3	is phenyl (or phenyl substituted by from one to three substituents selected from halogen, lower alkoxy, hydroxy, lower alkyl, nitro, amino, lower alkylamino, di-lower alkylamino, loweralkylmercapto, lower alkylsulfinyl, lower alkylsulfonyl and methylenedioxy), 2- or 4-biphenyl or 1- or 2-naphthyl (or 1- or 2-naphthyl substituted by from one to two substituents selected from lower alkyl, lower alkoxy, halogen, lower alkylmercapto, lower alkylsulfinyl, lower alkylsulfonyl and trifluoromethyl);
R_4	is hydrogen or from one to two substituents selected from loweralkyl, hydroxy, lower alkoxy, and halogen at the 4-, 5-, 6- or 7- positions;
Alk	is lower alkylene containing from two to four carbon atoms which may contain a lower alkyl group;
n	is 0 or 1;
Het	is an aliphatic heterocycle, 2-piperazinyl and 2-indolinyl.

The present compound differs from formula 3 primarily in having a carbonyl on the nitrogen of the indole.

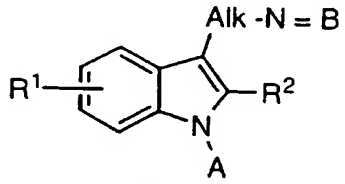
U.S. Patent 3,489,770 generically discloses compound having the following formula 4:



4

The compounds are said to have anti-inflammatory, hypotensive, hypoglycemic and CNS activities. Although not within the ambit of the above-defined genus, the patent also discloses a variety of species where R_2 is an arylcarbonyl group.

British Patent 1,374,414 and U.S. Patent 4,021,431 generically discloses compounds having the following structural formula 5:



5

The compounds are useful as anti-inflammatory agents. Although not within the ambit of the above-defined genus, the patent also discloses a variety of species where A is an arylcarbonyl group.

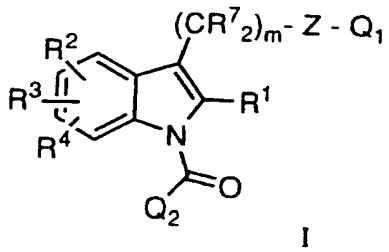
SUMMARY OF THE INVENTION

The present invention relates to indoles having activity on the cannabinoid receptor CB2 and the methods of their preparation.

Because of this activity on the cannabinoid receptor, the compounds of the present invention are useful for lowering the IOP (intra ocular pressure).

DETAIL DESCRIPTION OF THE INVENTION

The compounds of the invention can be summarized by formula I:



I

wherein:

R^1 is H, lower alkyl, aryl, benzyl, or lower fluorinated alkyl;

R^{2-4} is independently, H, lower alkyl, lower fluorinated alkyl, halogen, NO_2, CN, $-(CR^7_2)m-OR^1$, $-(CR^7_2)m-S(O)nR^6_2$, or $-(CR^7_2)m-R^6$;

R^5 is H, lower alkyl, aryl, or benzyl;

R^6 is lower alkyl, aryl, benzyl, or $N(R^5)_2$;

R^7 is H, or lower alkyl;

R^8 is R^7, lower fluorinated alkyl, halogen, OR^7, or lower alkyl thio;

R^9 is R^7, lower fluorinated alkyl, halogen, OR^7, or lower alkyl thio;

Q_1 is H, OR^7, CHO, CN, CO_2R^7, $C(O)SR^7$, $S(O)_nR^6$, HET or $N(R^7)_2$, wherein two R^7 groups may be joined to form a

pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine ring and their quaternary methyl ammonium salts;

Q_2 is phenyl, naphthyl, quinolinyl, furanyl, thienyl, pyridinyl, anthracyl, benzothienyl, benzofuranyl or thieno[3,2-b]-pyridinyl, mono-, di- or trisubstituted with R^8;

HET is is a diradical of benzene, thiazole, thiophene, or furan, substituted with one or two R^9 groups;

Z is CO or a bond.

m is 0-6; and

n is 0,1, or 2.

Definitions

The following abbreviations have the indicated meanings:

DCC	=	1,3-dicyclohexylcarbodiimide
DIBAL	=	diisobutyl aluminum hydride
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
HMPA	=	hexamethylphosphoramide
KHMDS	=	potassium hexamethyldisilazane
LDA	=	lithium diisopropylamide
MCPBA	=	metachloroperbenzoic acid
Ms	=	methanesulfonyl = mesyl
MsO	=	methanesulfonate = mesylate
NBS	=	N-bromosuccinimide
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
Ph	=	phenyl
PPTS	=	pyridinium p-toluene sulfonate
pTSA	=	p-toluene sulfonic acid
Pye	=	pyridinediyl

r.t.	=	room temperature
rac.	=	racemic
Tf	=	trifluoromethanesulfonyl = triflyl
TfO	=	trifluoromethanesulfonate = triflate
THF	=	tetrahydrofuran
THP	=	tetrahydropyran-2-yl
TLC	=	thin layer chromatography
Ts	=	p-toluenesulfonyl = tosyl
TsO	=	p-toluenesulfonate = tosylate
Tz	=	1H (or 2H)-tetrazol-5-yl
SO_2	=	=O=S=O

Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl

The term alkyl means linear, branched, and cyclic structures and combinations thereof.

"Lower alkyl" means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, s- and t-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclohexylmethyl, and the like.

"Lower alkoxy" means alkoxy groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

"Lower alkylthio" means alkylthio groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration.

Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies -$SCH_2CH_2CH_3$.

"Aryl" includes phenyl and phenyl monosubstituted by halogen, a lower alkoxy or a lower alkylthio group.

"Lower fluorinated alkyl" means alkyl groups of from 1 to 7 carbon atoms in which one or more of the hydrogen atoms has been replaced by fluorine.

"Benzyl" includes mono or disubstitution on the aromatic ring by halogen, lower alkoxy or lower alkylthio groups. The hydrogens of the methylene moiety could be replace by lower alkyl.

Halogen includes F, Cl, Br, and I.

It is intended that the definition of any substituent (e.g., R^5) in a particular molecule be independent of its definition elsewhere in the molecule. Thus, -$N(R^5)_2$ represents -NHH, -$NHCH_3$, -NHC_6H_5, etc.

Optical Isomers - Diastereomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Salts

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from

pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Examples of the novel compounds of this invention are as follows:

TABLE 1 *m = 1 EXCEPT NOTED OTHERWISE

CPD	R^1	R^2	R^3	R^4	R^7 *	Z	Q_1	Q_2
1	CH_3	H	H	Cl	H	-	4-MORPHOLINE	2-CHLOROPHENYL
2	CH_3	H	H	F	H	-	4-MORPHOLINE	2-CHLOROPHENYL
3	CH_3	H	H	Br	H	-	4- MORPHOLINE	2-CHLOROPHENYL
4	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	2-CHLOROPHENYL
5	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	2-CHLOROPHENYL
6	CH_3	H	H	C_2F_5	H	-	4-MORPHOLINE	2-CHLOROPHENYL
7	CH_3	H	H	NO_2	H	-	4- MORPHOLINE	2-CHLOROPHENYL
8	CH_3	H	H	Ph	H	-	4-MORPHOLINE	2-CHLOROPHENYL
9	CH_3	H	H	NH_2	H	-	4-MORPHOLINE	2-CHLOROPHENYL
10	CH_3	H	H	$N(CH_3)_2$	H	-	4-MORPHOLINE	2-CHLOROPHENYL
11	CH_3	H	H	$N(Bn)_2$	H	-	4- MORPHOLINE	2-CHLOROPHENYL
12	CH_3	H	H	$N(Ph)_2$	H	-	4-MORPHOLINE	2-CHLOROPHENYL
13	CH_3	H	H	CN	H	-	4-MORPHOLINE	2-CHLOROPHENYL
14	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	2-CHLOROPHENYL
15	CH_3	H	H	SO_2Ph	H	-	4-MORPHOLINE	2-CHLOROPHENYL
16	CH_3	H	H	SO_2NH_2	H	-	4-MORPHOLINE	2-CHLOROPHENYL
17	CH_3	H	H	SO_2NHCH_3	H	-	4-MORPHOLINE	2-CHLOROPHENYL
18	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	4-MORPHOLINE	2-CHLOROPHENYL
19	CH_3	H	H	CH_3	H	-	4-MORPHOLINE	2-CHLOROPHENYL
20	CH_3	H	H	C_2H_5	H	-	4-MORPHOLINE	2-CHLOROPHENYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
21	CH_3	H	H	n-C_3H_7	H	-	4-MORPHOLINE	2-CHLOROPHENYL
22	CH_3	H	H	OH	H	-	4-MORPHOLINE	2-CHLOROPHENYL
23	CH_3	H	H	OC_2H_5	H	-	4-MORPHOLINE	2-CHLOROPHENYL
24	CH_3	H	H	OC_3H_7	H	-	4-MORPHOLINE	2-CHLOROPHENYL
25	CH_3	H	H	OPh	H	-	4-MORPHOLINE	2-CHLOROPHENYL
26	CH_3	H	H	OBn	H	-	4-MORPHOLINE	2-CHLOROPHENYL
27	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	2-CHLOROPHENYL
28	CH_3	H	H	Cl	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
29	CH_3	H	H	F	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
30	CH_3	H	H	Br	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
31	CH_3	H	H	OCH_3	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
32	CH_3	H	H	CF_3	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
33	CH_3	H	H	C_2F_5	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
34	CH_3	H	H	NO_2	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
35	CH_3	H	H	Ph	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
36	CH_3	H	H	NH_2	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
37	CH_3	H	H	$N(CH_3)_2$	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
38	CH_3	H	H	$N(Bn)_2$	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
39	CH_3	H	H	$N(Ph)_2$	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
40	CH_3	H	H	CN	H	CO	4-MORPHOLINE	2-CHLOROPHENYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
41	CH_3	H	H	SO_2CH_3	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
42	CH_3	H	H	SO_2Ph	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
43	CH_3	H	H	SO_2NH_2	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
44	CH_3	H	H	SO_2NHCH_3	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
45	CH_3	H	H	$SO_2NCH_3)_2$	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
46	CH_3	H	H	CH_3	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
47	CH_3	H	H	C_2H_5	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
48	CH_3	H	H	n-C_3H_7	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
49	CH_3	H	H	OH	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
50	CH_3	H	H	OC_2H_5	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
51	CH_3	H	H	OC_3H_7	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
52	CH_3	H	H	OPh	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
53	CH_3	H	H	OBn	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
54	CH_3	H	H	OCF_3	H	CO	4-MORPHOLINE	2-CHLOROPHENYL
55	CH_3	H	H	H	H	-	4-MORPHOLINE	2,3-DICHLOROPHENYL
56	CH_3	H	H	F	H	-	4-MORPHOLINE	2,3-DICHLOROPHENYL
57	CH_3	H	H	Cl	H	-	4-MORPHOLINE	2,3-DICHLOROPHENYL
58	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	2,3-DICHLOROPHENYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
59	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	2,3-DICHLOROPHENYL
60	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	2,3-DICHLOROPHENYL
61	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	2,3-DICHLOROPHENYL
62	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	4-MORPHOLINE	2,3-DICHLOROPHENYL
63	CH_3	H	H	H	H	-	4-MORPHOLINE	1-NAPHTHYL
64	CH_3	H	H	F	H	-	4-MORPHOLINE	1-NAPHTHYL
65	CH_3	H	H	Cl	H	-	4-MORPHOLINE	1-NAPHTHYL
66	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	1-NAPHTHYL
67	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	1-NAPHTHYL
68	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	1-NAPHTHYL
69	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	1-NAPHTHYL
70	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	4-MORPHOLINE	1-NAPHTHYL
71	CH_3	H	H	H	H	-	4-MORPHOLINE	2-NAPHTHYL
72	CH_3	H	H	F	H	-	4-MORPHOLINE	2-NAPHTHYL
73	CH_3	H	H	Cl	H	-	4-MORPHOLINE	2-NAPHTHYL
74	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	2-NAPHTHYL
75	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	2-NAPHTHYL
76	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	2-NAPHTHYL
77	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	2-NAPHTHYL
78	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	4-MORPHOLINE	2-NAPHTHYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
79	CH_3	H	H	H	H	-	4-MORPHOLINE	2-THIENYL
80	CH_3	H	H	F	H	-	4-MORPHOLINE	2-THIENYL
81	CH_3	H	H	Cl	H	-	4-MORPHOLINE	2-THIENYL
82	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	2-THIENYL
83	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	2-THIENYL
84	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	2-THIENYL
85	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	2-THIENYL
86	CH_3	H	H	$SO_2N(CH_3)2$	H	-	4-MORPHOLINE	2-THIENYL
87	CH_3	H	H	H	H	-	4-MORPHOLINE	5-CHLORO-2-THIENYL
88	CH_3	H	H	F	H	-	4-MORPHOLINE	5-CHLORO-2-THIENYL
89	CH_3	H	H	Cl	H	-	4-MORPHOLINE	5-CHLORO-2-THIENYL
90	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	5-CHLORO-2-THIENYL
91	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	5-CHLORO-2-THIENYL
92	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	5-CHLORO-2-THIENYL
93	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	5-CHLORO-2-THIENYL
94	CH_3	H	H	$SO_2N(CH_3)2$	H	-	4-MORPHOLINE	5-CHLORO-2-THIENYL
95	CH_3	H	H	H	H	-	4-MORPHOLINE	3,4,5-TRICHLORO-2-THIENYL
96	CH_3	H	H	F	H	-	4-MORPHOLINE	3,4,5-TRICHLORO-2-THIENYL
97	CH_3	H	H	Cl	H	-	4-MORPHOLINE	3,4,5-TRICHLORO-2-THIENYL
98	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	3,4,5-TRICHLORO-2-THIENYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
99	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	3,4,5-TRICHLORO-2-THIENYL
100	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	3,4,5-TRICHLORO-2-THIENYL
101	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	3,4,5-TRICHLORO-2-THIENYL
102	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	4-MORPHOLINE	3,4,5-TRICHLORO-2-THIENYL
103	CH_3	H	H	H	H	-	4-MORPHOLINE	2-FURANYL
104	CH_3	H	H	F	H	-	4-MORPHOLINE	2-FURANYL
105	CH_3	H	H	Cl	H	-	4-MORPHOLINE	2-FURANYL
106	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	2-FURANYL
107	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	2-FURANYL
108	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	2-FURANYL
109	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	2-FURANYL
110	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	4-MORPHOLINE	2-FURANYL
111	CH_3	H	H	H	H	-	4-MORPHOLINE	5-CHLORO-2-FURANYL
112	CH_3	H	H	F	H	-	4-MORPHOLINE	5-CHLORO-2-FURANYL
113	CH_3	H	H	Cl	H	-	4-MORPHOLINE	5-CHLORO-2-FURANYL
114	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	5-CHLORO-2-FURANYL
115	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	5-CHLORO-2-FURANYL
116	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	5-CHLORO-2-FURANYL
117	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	5-CHLORO-2-FURANYL
118	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	4-MORPHOLINE	5-CHLORO-2-FURANYL

TABLE 1 (CONTINUED)

CPD	R1	R2	R3	R4	R7*	Z	Q1	Q2
119	CH_3	H	H	H	H	-	4-MORPHOLINE	3-FURANYL
120	CH_3	H	H	F	H	-	4-MORPHOLINE	3-FURANYL
121	CH_3	H	H	Cl	H	-	4-MORPHOLINE	3-FURANYL
122	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	3-FURANYL
123	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	3-FURANYL
124	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	3-FURANYL
125	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	3-FURANYL
126	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	4-MORPHOLINE	3-FURANYL
127	CH_3	H	H	H	H	-	4-MORPHOLINE	3-THIENYL
128	CH_3	H	H	F	H	-	4-MORPHOLINE	3-THIENYL
129	CH_3	H	H	Cl	H	-	4-MORPHOLINE	3-THIENYL
130	CH_3	H	H	OCH_3	H	-	4-MORPHOLINE	3-THIENYL
131	CH_3	H	H	OCF_3	H	-	4-MORPHOLINE	3-THIENYL
132	CH_3	H	H	CF_3	H	-	4-MORPHOLINE	3-THIENYL
133	CH_3	H	H	SO_2CH_3	H	-	4-MORPHOLINE	3-THIENYL
134	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	4-MORPHOLINE	3-THIENYL
135	CH_3	H	H	H	H	-	1-PIPERIDINYL	2-CHLOROPHENYL
136	CH_3	H	H	F	H	-	1-PIPERIDINYL	2-CHLOROPHENYL
137	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	2-CHLOROPHENYL
138	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	2-CHLOROPHENYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
139	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	2-CHLOROPHENYL
140	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	2-CHLOROPHENYL
141	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	2-CHLOROPHENYL
142	CH_3	H	H	$SO_2N(CH_3)2$	H	-	1-PIPERIDINYL	2-CHLOROPHENYL
143	CH_3	H	H	H	H	-	1-PIPERIDINYL	2,3-DICHLOROPHENYL
144	CH_3	H	H	F	H	-	1-PIPERIDINYL	2,3-DICHLOROPHENYL
145	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	2,3-DICHLOROPHENYL
146	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	2,3-DICHLOROPHENYL
147	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	2,3-DICHLOROPHENYL
148	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	2,3-DICHLOROPHENYL
149	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	2,3-DICHLOROPHENYL
150	CH_3	H	H	$SO_2N(CH_3)2$	H	-	1-PIPERIDINYL	2,3-DICHLOROPHENYL
151	CH_3	H	H	H	H	-	1-PIPERIDINYL	1-NAPHTHYL
152	CH_3	H	H	F	H	-	1-PIPERIDINYL	1-NAPHTHYL
153	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	1-NAPHTHYL
154	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	1-NAPHTHYL
155	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	1-NAPHTHYL
156	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	1-NAPHTHYL
157	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	1-NAPHTHYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
158	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	1-PIPERIDINYL	1-NAPHTHYL
159	CH_3	H	H	H	H	-	1-PIPERIDINYL	2-NAPHTHYL
160	CH_3	H	H	F	H	-	1-PIPERIDINYL	2-NAPHTHYL
161	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	2-NAPHTHYL
162	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	2-NAPHTHYL
163	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	2-NAPHTHYL
164	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	2-NAPHTHYL
165	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	2-NAPHTHYL
166	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	1-PIPERIDINYL	2-NAPHTHYL
167	CH_3	H	H	H	H	-	1-PIPERIDINYL	2-THIENYL
168	CH_3	H	H	F	H	-	1-PIPERIDINYL	2-THIENYL
169	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	2-THIENYL
170	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	2-THIENYL
171	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	2-THIENYL
172	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	2-THIENYL
173	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	2-THIENYL
174	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	1-PIPERIDINYL	2-THIENYL
175	CH_3	H	H	H	H	-	1-PIPERIDINYL	5-CHLORO-2-THIENYL
176	CH_3	H	H	F	H	-	1-PIPERIDINYL	5-CHLORO-2-THIENYL
177	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	5-CHLORO-2-THIENYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
178	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	5-CHLORO-2-THIENYL
179	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	5-CHLORO-2-THIENYL
180	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	5-CHLORO-2-THIENYL
181	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	5-CHLORO-2-THIENYL
182	CH_3	H	H	$SO_2N(CH_3)2$	H	-	1-PIPERIDINYL	5-CHLORO-2-THIENYL
183	CH_3	H	H	H	H	-	1-PIPERIDINYL	3,4,5-TRICHLORO-2-THIENYL
184	CH_3	H	H	F	H	-	1-PIPERIDINYL	3,4,5-TRICHLORO-2-THIENYL
185	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	3,4,5-TRICHLORO-2-THIENYL
186	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	3,4,5-TRICHLORO-2-THIENYL
187	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	3,4,5-TRICHLORO-2-THIENYL
188	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	3,4,5-TRICHLORO-2-THIENYL
189	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	3,4,5-TRICHLORO-2-THIENYL
190	CH_3	H	H	$SO_2N(CH_3)2$	H	-	1-PIPERIDINYL	3,4,5-TRICHLORO-2-THIENYL
191	CH_3	H	H	H	H	-	1-PIPERIDINYL	2-FURANYL
192	CH_3	H	H	F	H	-	1-PIPERIDINYL	2-FURANYL
193	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	2-FURANYL
194	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	2-FURANYL
195	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	2-FURANYL
196	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	2-FURANYL
197	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	2-FURANYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
198	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	1-PIPERIDINYL	2-FURANYL
199	CH_3	H	H	H	H	-	1-PIPERIDINYL	3-FURANYL
200	CH_3	H	H	F	H	-	1-PIPERIDINYL	3-FURANYL
201	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	3-FURANYL
202	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	3-FURANYL
203	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	3-FURANYL
204	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	3-FURANYL
205	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	3-FURANYL
206	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	1-PIPERIDINYL	3-FURANYL
207	CH_3	H	H	H	H	-	1-PIPERIDINYL	5-CHLORO-2-FURANYL
208	CH_3	H	H	F	H	-	1-PIPERIDINYL	5-CHLORO-2-FURANYL
209	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	5-CHLORO-2-FURANYL
210	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	5-CHLORO-2-FURANYL
211	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	5-CHLORO-2-FURANYL
212	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	5-CHLORO-2-FURANYL
213	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	5-CHLORO-2-FURANYL
214	CH_3	H	H	$SO_2N(CH_3)_2$	H	-	1-PIPERIDINYL	5-CHLORO-2-FURANYL
215	CH_3	H	H	H	H	-	1-PIPERIDINYL	3-THIENYL
216	CH_3	H	H	F	H	-	1-PIPERIDINYL	3-THIENYL
217	CH_3	H	H	Cl	H	-	1-PIPERIDINYL	3-THIENYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
218	CH_3	H	H	OCH_3	H	-	1-PIPERIDINYL	3-THIENYL
219	CH_3	H	H	OCF_3	H	-	1-PIPERIDINYL	3-THIENYL
220	CH_3	H	H	CF_3	H	-	1-PIPERIDINYL	3-THIENYL
221	CH_3	H	H	SO_2CH_3	H	-	1-PIPERIDINYL	3-THIENYL
222	H	H	H	$SO_2N(CH_3)_2$	H	-	1-PIPERIDINYL	3-THIENYL
223	H	H	H	Cl	H	-	$(CH_3)_3N^+$	2-CHLOROPHENYL
224	H	H	H	OCH_3	H	-	$(CH_3)_3N^+$	2,3-DICHLOROPHENYL
225	H	H	H	Cl	H	-	2-PYRIDINYL	2-CHLOROPHENYL
226	H	H	H	OCH_3	H	-	2-PYRIDINYL	2,3-DICHLOROPHENYL
227	H	H	H	Cl	H	-	1-PYRROLIDINYL	9-ANTHRACYL
228	H	H	H	OCH_3	H	-	1PYRROLIDINYL	9-ANTHRACYL
229	H	H	H	Cl	H	-	2-PYRIDINYL	2-CHLOROPHENYL
230	H	H	H	OCH_3	H	-	2-PYRIDINYL	2,3-DICHLOROPHENYL
231	H	H	H	Cl	H	-	2-PYRROLIDINYL	9-ANTHRACYL
232	H	H	H	OCH_3	H	-	2-PYRROLIDINYL	9-ANTHRACYL
233	H	H	H	Cl	H	-	1-PIPERAZINYL	2-CHLOROPHENYL
234	H	H	H	OCH_3	H	-	2-PIPERAZINYL	2,3-DICHLOROPHENYL
235	H	H	H	Cl	H	-	PHENYL	9-ANTHRACYL
236	CH_3	H	H	OCH_3	H	-	PHENYL	2-CHLOROPHENYL
237	CH_3	H	H	Cl	H	-	PHENYL	2,3-DICHLOROPHENYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
238	CH_3	H	H	OCH_3	H	-	2-CHLOROPHENYL	9-ANTHRACYL
239	CH_3	H	H	Cl	H	-	2,3-DICHLOROPHENYL	2-CHLOROPHENYL
240	CH_3	H	H	OCH_3	H	-	2-THIENYL	2,3-DICHLOROPHENYL
241	CH_3	H	H	Cl	H	-	3-THIENYL	2-CHLOROPHENYL
242	CH_3	H	H	OCH_3	H	CO	1-PIPERIDINYL	2-CHLOROPHENYL
243	CH_3	H	H	Cl	H	CO	1-PIPERIDINYL	2,3-DICHLOROPHENYL
244	CH_3	H	H	OCH_3	H	CO	1-PIPERIDINYL	9-ANTHRACYL
245	CH_3	H	H	Cl	H	CO	1-PIPERIDINYL	2-THIENYL
246	CH_3	H	H	OCH_3	H	CO	1-PIPERIDINYL	3-THIENYL
247	CH_3	H	H	Cl	H	CO	1-PIPERIDINYL	2-FURANYL
248	CH_3	H	H	OCH_3	H	CO	1-PIPERIDINYL	3-FURANYL
249	CH_3	H	H	Cl	H	CO	1-PIPERIDINYL	1-NAPHTHYL
250	CH_3	H	H	OCH_3	H	CO	1-PIPERIDINYL	2-NAPHTHYL
251	CH_3	H	H	Cl	H	CO	1-PYRROLIDINYL	2-CHLOROPHENYL
252	CH_3	H	H	OCH_3	H	CO	1-PYRROLIDINYL	2,3-DICHLOROPHENYL
253	CH_3	H	H	Cl	H	CO	1-PYRROLIDINYL	9-ANTHRACYL
254	CH_3	H	H	OCH_3	H	CO	1-PYRROLIDINYL	2-THIENYL
255	CH_3	H	H	Cl	H	CO	1-PYRROLIDINYL	3-THIENYL
256	CH_3	H	H	OCH_3	H	CO	1-PYRROLIDINYL	2-FURANYL
257	CH_3	H	H	H	H	CO	4-MORPHOLINE	1-NAPHTHYL

TABLE 1 (CONTINUED)

CPD	R^1	R^2	R^3	R^4	R^{7*}	Z	Q_1	Q_2
258	CH_3	H	H	OCH_3	H	CO	4-MORPHOLINE	2,5-DICHLOROPHENYL
259	CH_3	H	H	OCH_3	H	CO	4-MORPHOLINE	2,3-DICHLOROPHENYL
260	CH_3	H	H	OCH_3	H	CO	4-MORPHOLINE	2-CHLORO-4FLUOROPHENYL
261	CH_3	H	H	OCH_3	H	CO	4-MORPHOLINE	3-CHLOROPHENYL
262	CH_3	H	H	H	H	-	$COOCH_3$	1-NAPHTHYL
263	CH_3	H	H	H	H(m=2)	-	4-MORPHOLINE	1-NAPHTHYL
264	CH_3	H	H	OCH_3	H(m=2)	-	4-MORPHOLINE	2,3-DICHLOROPHENYL
265	CH_3	H	H	H	H	-	4-MORPHOLINE	2-CHLOROPHENYL
266	CH_3	H	H	OCH_3	H(m=2)	-	4-MORPHOLINE	1-NAPHTHYL
267	CH_3	H	H	OCH_3	H(m=2)	-	4-MORPHOLINE	2-CHLOROPHENYL
268	CH_3	H	H	H	H(m=2)	-	4-MORPHOLINE	2-CHLOROPHENYL

Elemental analysis was conducted on several of the compounds listed above and the results are shown below.

TABLE 2

ELEMENTAL ANALYSIS							
		CALCULATED			FOUND		
CPD	FORMULA	C	H	N	C	H	N
31	$C_{23}H_{23}ClN_2O_4$	64.71	5.43	6.56	64.78	5.69	6.42
63	$C_{25}H_{23}ClN_2O_2$	71.33	5.99	6.65	71.23	6.99	6.57
258	$C_{23}H_{22}Cl_2N_2O_4$	59.88	4.81	6.07	59.56	4.86	6.09
259	$C_{23}H_{22}Cl_2N_2O_4$	59.88	4.81	6.07	59.25	4.89	5.81
260	$C_{23}H_{22}ClFN_2O_4$	62.09	4.98	6.30	62.05	5.04	6.53
261	$C_{23}H_{23}ClN_2O_4$	64.71	5.43	6.56	63.36	5.29	6.47
263	$C_{26}H_{27}ClN_2O_2$	71.80	6.26	6.44	71.64	6.36	6.15

The preferred compounds are realized when:

R^1 is	H, lower alkyl, or lower fluorinated alkyl;
R^{2-4} is	independently H, lower alkyl, OR^1, halogen, or lower fluorinated alkyl;
R^7 is	H, or lower alkyl; and
Q_1 is	morpholine, piperazine, piperidine, or pyrrolidine.

The most preferred compounds are realized when:

R^1 is	lower alkyl;
R^{2-4} is	independently is H, or OR^1;
R^7 is	H;
Q_1 is	morpholine;
m is	2; and
Z is	a bond.

Specific compounds are:

2-[1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]ethanone;

2-Methyl-3-(morpholin-4-yl)methyl-1-(1-naphthoyl)-1H-indole;

2-Methyl-1-(1-naphthoyl)-1H-indol-3-ylacetic acid, methyl ester;

1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)- 1*H*-indole;

1-(1-Naphthoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole;

1-(2-Chlorobenzoyl)-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(1-Naphthoyl)-5-Methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole;

1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole; and

1-(2-Chlorobenzoyl)-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole.

Utilities

The ability of the compounds of formula I to mimic the actions of the cannabinoids makes them useful for preventing or reversing the symptoms that can be treated with cannabis, some of its derivatives and synthetic cannabinoids in a human subject. Thus, compounds of formula I are useful to treat, prevent, or ameliorate in mammals and especially in humans:

1- various ocular disorders such as glaucoma.
2- pulmonary disorders including diseases such as asthma, chronic bronchitis and related airway diseases.
3- allergies and allergic reactions such as allergic rhinitis, contact dermatitis, allergic conjunctivitis and the like.
4- inflammation such as arthritis or inflammatory bowel disease.
5- pain.
6- disorders of the immune system such as lupus, AIDS, etc.
7- allograft rejection.
8- central nervous system diseases such as Tourette's syndrome, Parkinson's disease, Huntingdon's disease, epilepsy, various psychotic afflictions such as depression, manic depression, etc.
9- vomiting, and nausea and vertigo, especially in the case of chemotherapy patients.

Dose Ranges

The magnitude of therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration and vary upon the clinician's judgment. It will also vary according to the age, weight and response of the individual patient. An effective dosage amount of the active component can thus be determined by the clinician after a consideration of all the criteria and using is best judgment on the patient's behalf.

An ophthalmic preparation for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compounds of Formula I in an acceptable ophthalmic formulation may be used.

Pharmaceutical Compositions

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, parenteral and topical may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, parenteral and ocular (ophthalmic). They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a

pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by

molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

Combinations with Other Drugs

In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients or prodrugs thereof. These other active species may be beta-blockers such as timolol, topical carbonic anhydrase inhibitors such as Dorzolamide, systemic carbonic anhydrase inhibitors such as acetolamide, cholinergic agents such as pilocarpine and its derivatives, prostaglandin F receptor agonists such as Latanoprost, ajmaline and its derivatives, b2 adrenergic agonists such as epinephrine, glutamate antagonists, aminosteroids, diuretics, and any other compound used alone or in combination in the treatment of glaucoma. The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with a b-blockers, a carbonic anhydrase inhibitor, a pilocarpine derivative or a prostaglandin agonist, the weight ratio of the compound of the Formula I to the other drug will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

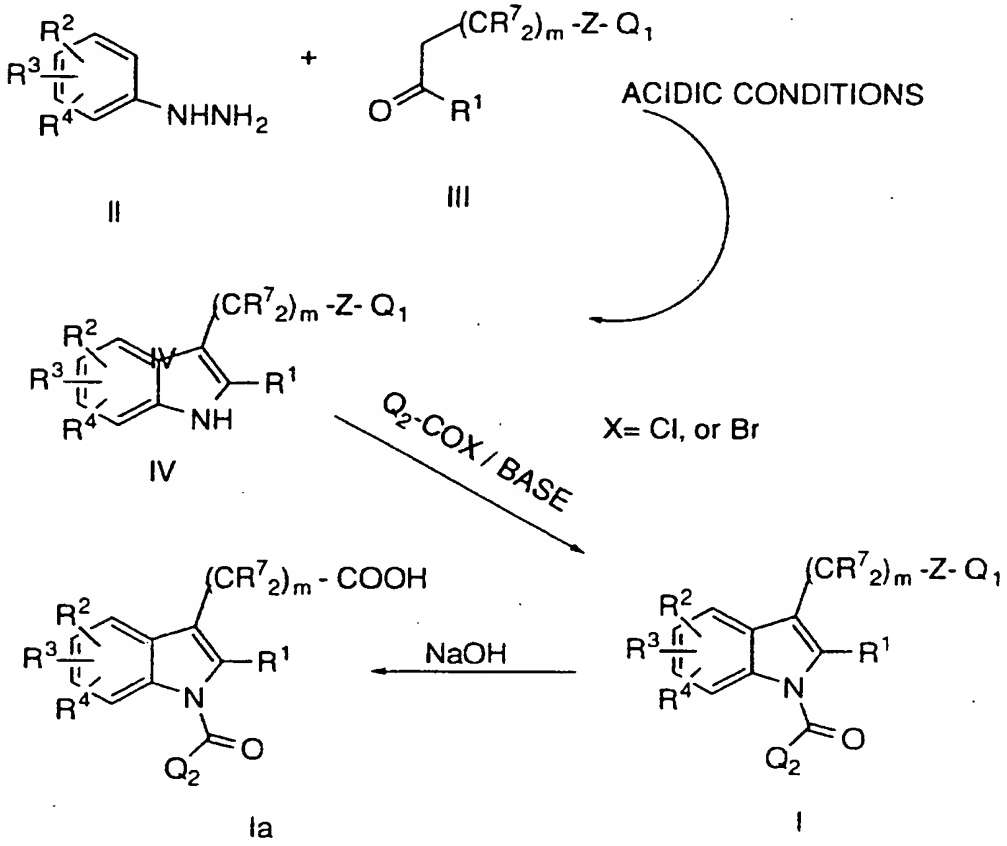
Methods of Synthesis

Compounds of the present invention can be prepared according to the following non-limiting methods. Temperatures are in degrees Celsius.

Method A

The starting indoles used are either commercially available or prepared from an appropiate hydrazine II and a properly substituted aldehyde or ketone III as described in U.S. patent 3,161,654 (incorporated herein). The indole IV obtained is then treated with an acyl chloride or bromide of a properly substituted Q2 and a base to afford the desired indole I. When Z-Q^1 is an ester, it can be hydrolysed to the desired acid Ia with a base such as 1N NaOH in a protic solvent such as MeOH-H_2O.

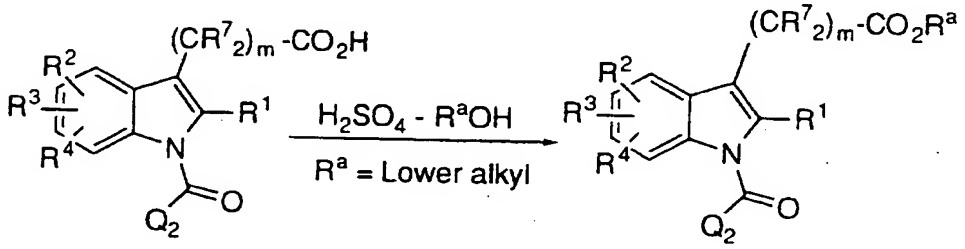
METHOD A



Method B

The acids Ia can be converted to a variety of esters Ib by dissolution in the appropriate lower alkyl alcohol with a strong acid such as 10% H_2SO_4 and heated between 60-90° C for 3-12h (Fischer conditions).

METHOD B

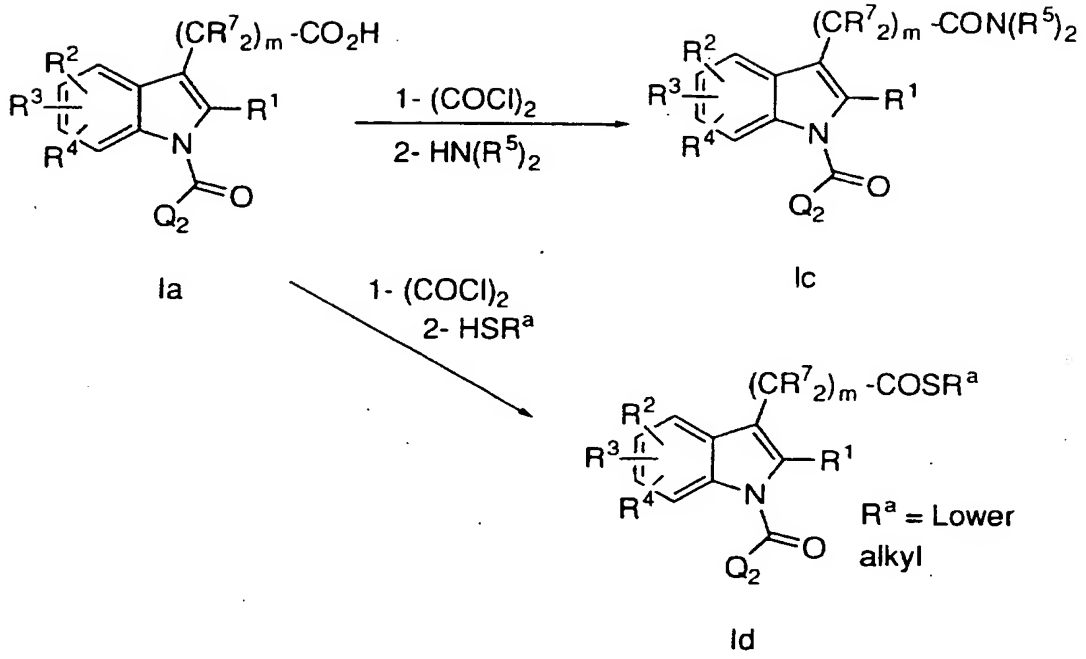


Ia Ib

Method C

Acids Ia are treated with a chlorinating agent such as oxalyl chloride in an inert solvent (methylene chloride, dichloroethane, etc.). The resulting acyl halide is then treated with amines or thiols in the presence of a base (excess amine, Et3N, etc.) to afford the corresponding amide Ic or thiol ester Id.

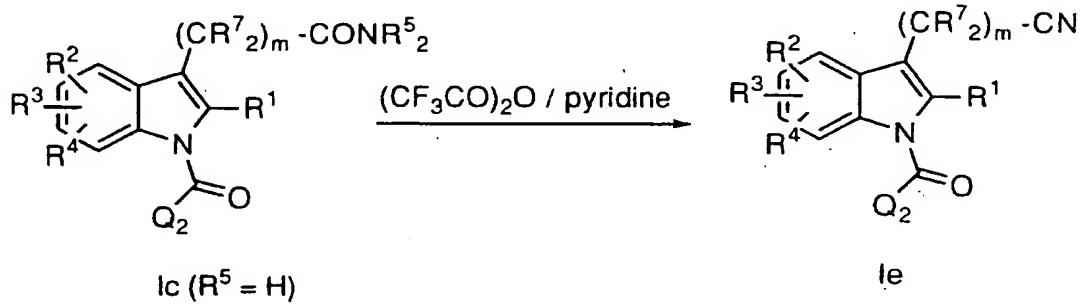
METHOD C



Method D

The primary amides of Ic in an inert solvent such as THF, Et_2O, etc. and a base such as pyridine are treated with a dehydrating agent such as trifluoroacetic anhydride at 0° C to afford the nitrile Ie.

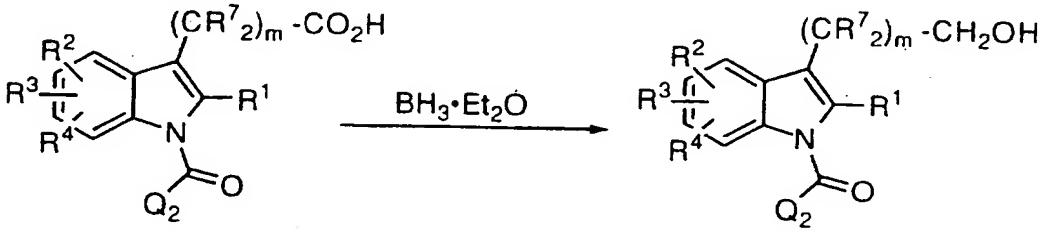
METHOD D



Method E

Acids Ia are treated with borane according to the literature (J.Org. Chem. 1973, **38**, 2786) to afford the alcohols If.

METHOD E

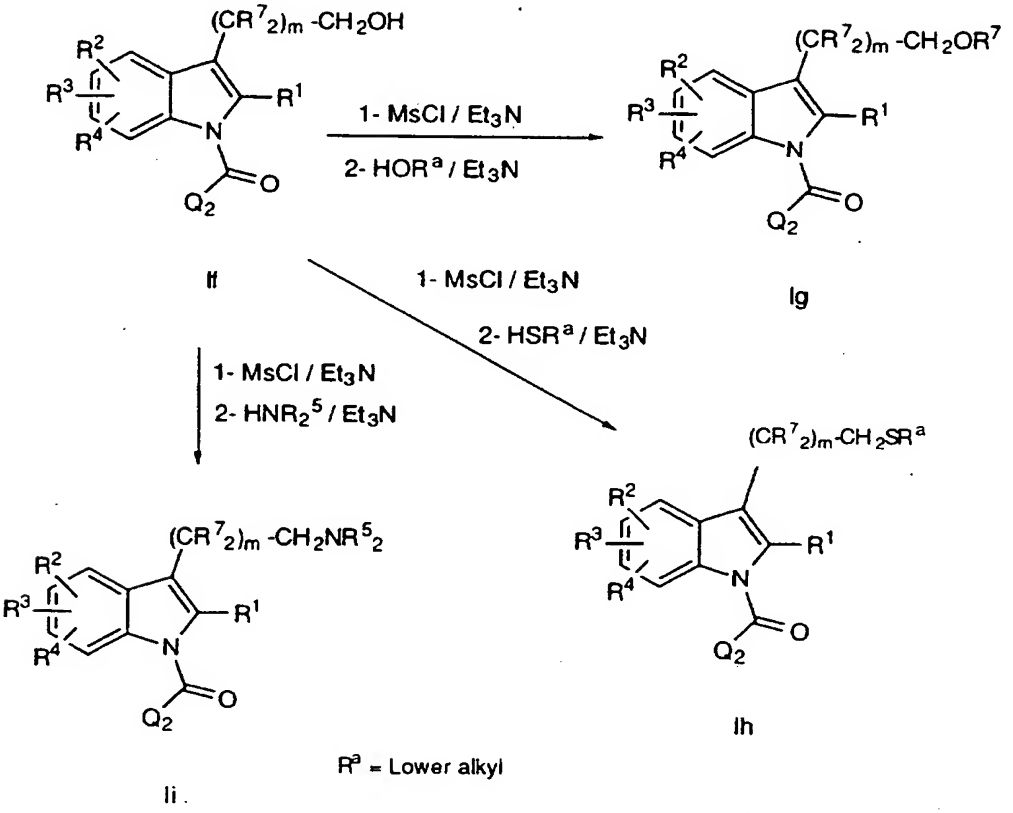


Ia If

Method F

Compounds of type If can be converted to their mesylate or tosylate in an inert solvent such as CH_2Cl_2 in the presence of a base such as Et_3N and then reacted with various nucleophiles such as alcohols, thiols and amines to produce compounds Ig, Ih and Ii.

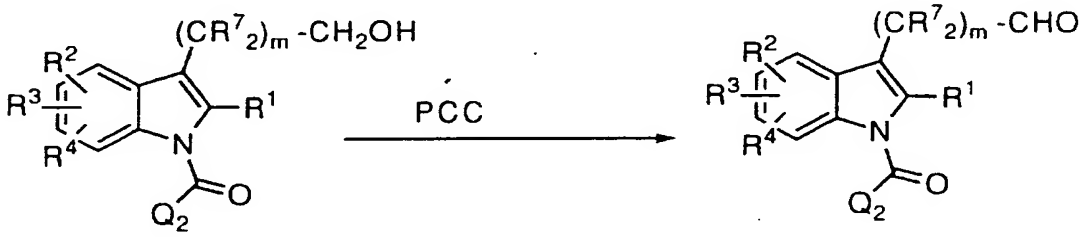
METHOD F



Method G

When compounds of type If are subjected to Swern oxidation (J. Org. Chem. 1978, **43**, 2480), with PCC (Tetrahedron Lett. 1975, 2647) or other oxidizing agents, aldehyde Ij is obtained.

METHOD G

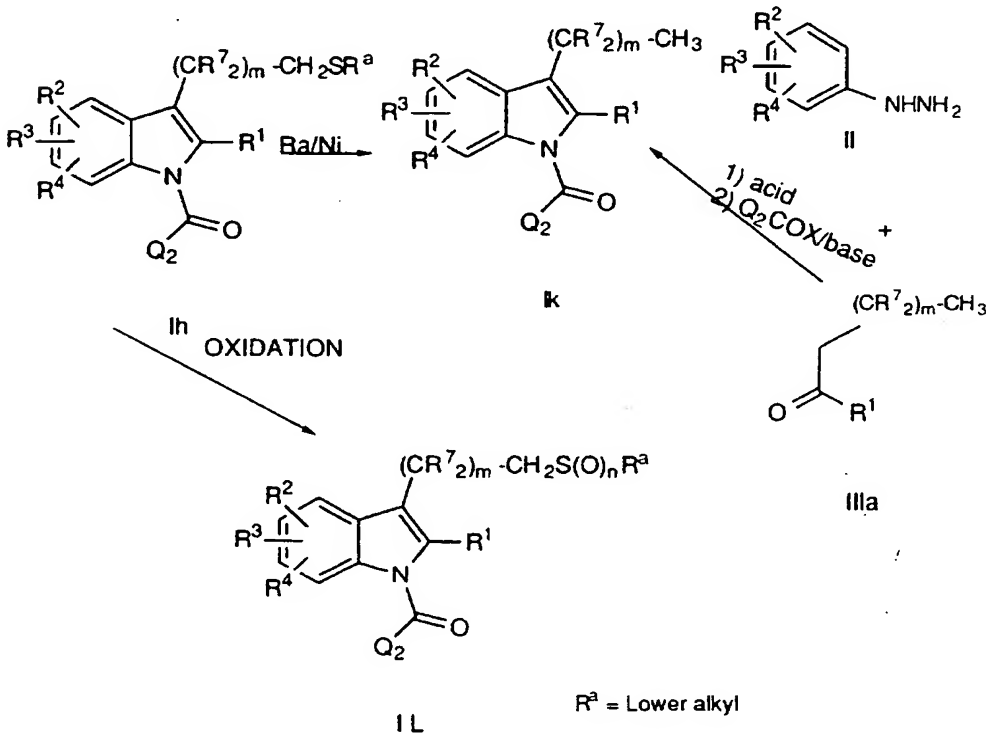


If Ij

Method H

Compounds of type Ih can be reduced to the alkyl chain by reaction with Raney-Nickel in a protic solvent such as ethanol to afford Ik, which can also be prepared by a Fischer indole synthesis starting with an appropriate hydrazine II and a ketone or aldehyde IIIa under acidic conditions. Compound Ih can be oxidized to the sulfoxide or sulfone using for example H_2O_2 or MCPBA to give Il.

METHOD H



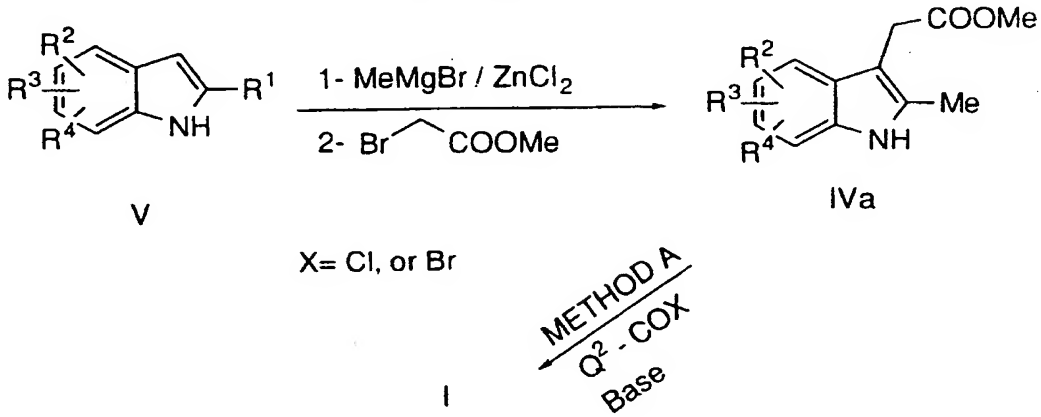
Il

R^a = Lower alkyl

Method I

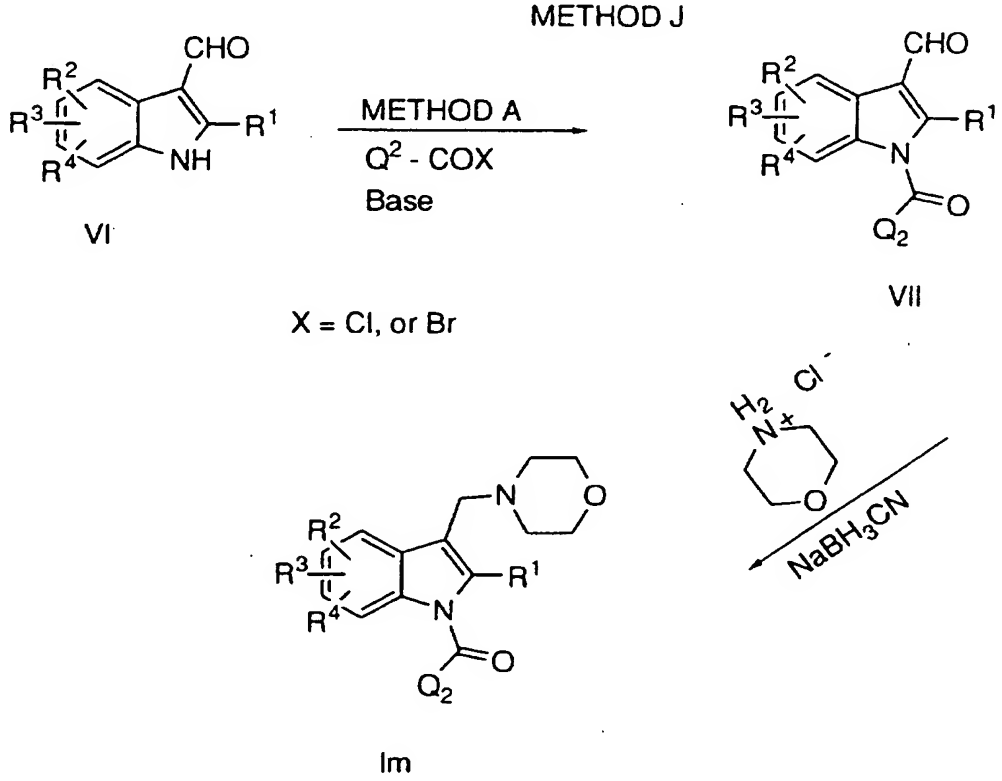
An indole of type V can be deprotonated with a strong base such as MeMgBr, treated with $ZnCl_2$ to exchange the metal when necessary, and an alkylating agent or (other electrophile) added to the mixture to yield compound of type IVa. This in turn according to method A can be converted to a compound of type I.

METHOD I



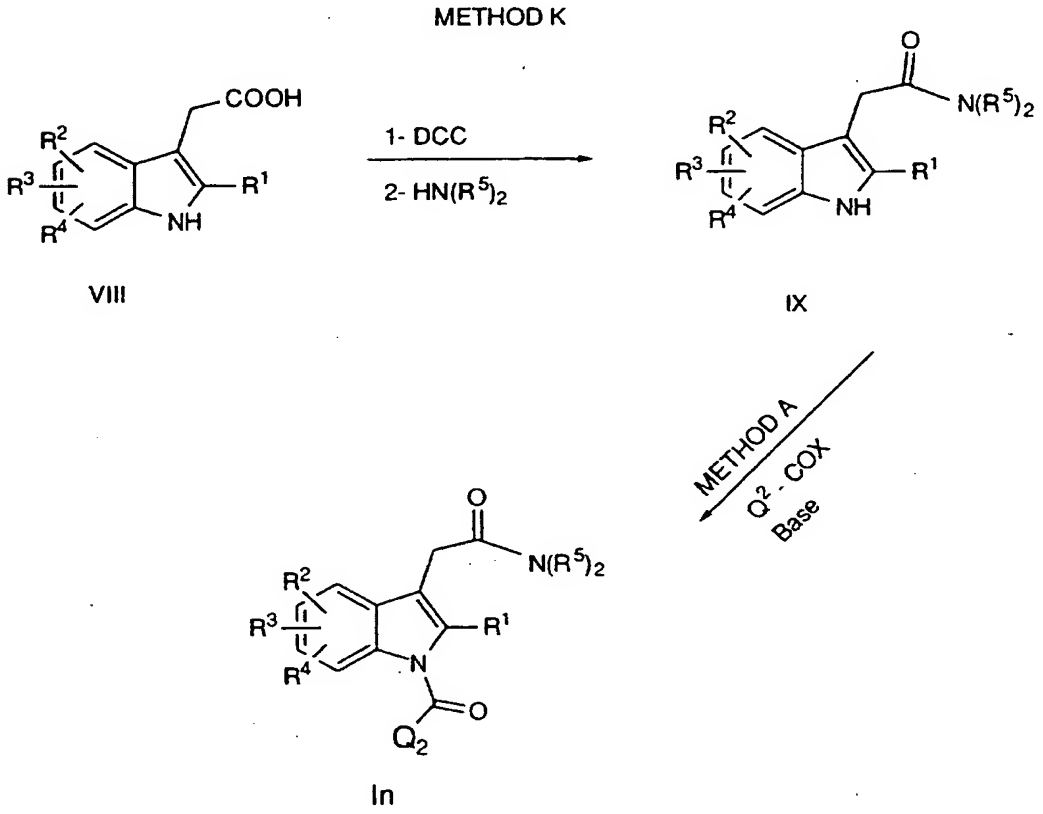
Method J

An indole of type VI can be treated according to method A to yield VII which can be converted to Im with an amine in presence of a reducing agent such as $NaBH_3CN$.



Method K

A carboxylic acidic of type VIII can be coupled with various amines in an inert solvent such as CH_2Cl_2 using DCC or the like to yield IX, which can then be converted to In according to method A.



The invention will now be illustrated by the following non-limiting examples (Note: The examples in Table 1, above, that are not illustrated can be made by substantially similar procedures as discussed below) in which, unless stated otherwise:

(i) all operations are carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;

(ii) evaporation of solvent is carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) the course of reactions is followed by thin layer chromatography (TLC) and reaction times are given for illustration only;

(iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(v) the structure and purity of all final products are assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry, or microanalytical data;

(vi) yields are given for illustration only;

(vii) when given, NMR data are in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent: conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings: the following abbreviations have also been used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL

INTERNATIONAL SEARCH REPORT

Interr. al Application No
PCT/CA 96/00080

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0105996	25-04-84	NONE		
US-A-3501465	17-03-70	CH-A-	485718	15-02-70
		DE-A-	1595940	12-02-70
		FR-M-	5205	03-07-67
		FR-A-	1472042	24-05-67
		GB-A-	1109884	
		NL-A-	6508553	03-01-66
US-A-3489770	13-01-70	US-A-	3481953	02-12-69
		US-A-	3487091	30-12-69
		US-A-	3489429	13-01-70
		US-A-	3494920	10-02-70
EP-A-0444451	04-09-91	US-A-	5068234	26-11-91
		AU-B-	638795	08-07-93
		AU-B-	7122291	29-08-91
		CA-A-	2035711	27-08-91
		IL-A-	97313	31-07-95
		JP-A-	7041475	10-02-95
		NO-B-	177006	27-03-95
		US-A-	5324737	28-06-94
US-A-3336194	15-08-67	BE-A-	647413	30-10-64
		CH-A-	460779	
		CH-A-	462169	
		FR-A-	1567853	23-05-69
		GB-A-	1058984	
		NL-A-	6404781	02-11-64
		US-A-	3285908	15-11-66
GB-A-2283745	17-05-95	US-A-	5436265	25-07-95

INTERNATIONAL SEARCH REPORT

[n' tional application No.

PCT/CA96/00080

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-7 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The search for claims 1 and 2 resulted in a large number of novelty destroying compounds. The search for these claims was not complete for economical reasons. (Claims 1 and 2 have been searched incompletely)

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/CA 96/00080

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 444 451 (STERLING DRUG INC) 4 September 1991 cited in the application see claims	1-4
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 16, no. 2, 1973 WASHINGTON US, pages 176-177, E.W. GLAMKOWSKI 'The aldehyde analog of indomethacin' see the whole document	1
X	US,A,3 336 194 (TSUNG-YIN SHEN ET AL.) 15 August 1967 see claims; examples	1-3
P,X	GB,A,2 283 745 (MERCK FROSST CANADA INC) 17 May 1995 see claims; examples	1-4
X	DATABASE CROSSFIRE Beilstein BRN=156339 & CHEM. BER., vol. 46, 1913 page 657 WEISSGERBER	1
X	DATABASE CROSSFIRE Beilstein BRN=448371 & ES,A,341 692 (GALLARDO S.A.) 1967	1,2
X	DATABASE CROSSFIRE Beilstein BRN=447300 & NL,A,6 404 781 (MERCK) 1964	1
X	DATABASE CROSSFIRE Beilstein BRN=451740 & US,A,3 161 654 (MERCK) 1963	1
X	DATABASE CROSSFIRE Beilstein BRN=493436 & BE,A,615 395 (MERCK) 1962	1
X	DATABASE CROSSFIRE Beilstein BRN=477362 & JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, 1973 LETCHWORTH GB, pages 13-14,	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/CA 96/00080

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/14 A61K31/40 A61K31/405 C07D209/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 105 996 (MERCK & CO INC) 25 April 1984 see claim 1: Metindol = 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-Indole-3-acetic acid ---	1-4
X	US,A,3 501 465 (SHEN TSUNG-YING ET AL) 17 March 1970 see claims; examples ---	1
X	US,A,3 489 770 (HERBST DAVID R) 13 January 1970 cited in the application see claims; examples --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 April 1996	17.04.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

13. Use of a compound of formula (I), as defined in Claim 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof, or a diastereomer or enantiomer or mixtures thereof in the manufacture of a cannabimimetic pharmacological agent selective for CB2 receptors.

bowel disease; pain; disorders of the immune system such as lupus, or AIDS; allograft rejection; central nervous system diseases such as Tourette's syndrome, or Parkinson's disease, or Huntingdon's disease, or epilepsy, or depression, or manic depression; vomiting; or nausea and vertigo; in mammals, including humans, in need thereof, which comprises administering to such a mammal a pharmacologically effective amount of a compound of Claim 1.

8. A composition useful for treating ocular hypertension and glaucoma in a mammal, including humans, in need thereof, which comprises a pharmacologically effective amount of a cannabimimetic pharmacological agent, known to be selective for CB2 receptors, in a carrier or diluent buffered to a pH suitable for ocular administration.

9. A composition useful for treating ocular hypertension and glaucoma in a mammal, including humans, in need thereof, which comprises a pharmacologically effective amount of a cannabimimetic pharmacological agent of Claim 1, known to be selective for CB2 receptors, in a carrier or diluent buffered to a pH suitable for ocular administration.

10. An ocular hypertension and glaucoma pharmaceutical composition comprising a pharmacologically effective amount of a compound of formula (I), as defined in Claim 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof, or a diastereomer or enantiomer or mixtures thereof, in association with a pharmaceutically acceptable carrier.

11. A compound of formula (I), as defined in Claim 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof, or a diastereomer or enantiomer or mixtures thereof, for use in treating ocular hypertension and glaucoma; pulmonary disorders; allergies and allergic reactions; or inflammation; pain; disorders of the immune system; allograft rejection; central nervous system diseases; vomiting; or nausea and vertigo.

12. Use of a compound of formula (I), as defined in Claim 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof, or a diastereomer or enantiomer or mixtures thereof as a cannabimimetic pharmacological agent selected for CB2 receptors.

1-(2,3-Dichlorobenzoyl)-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)- 1*H*-indole;

1-(1-Naphthoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole;

1-(2-Chlorobenzoyl)-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

1-(1-Naphthoyl)-5-Methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole;

1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole; or

1-(2-Chlorobenzoyl)-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1*H*-indole.

5. A method of treating ocular hypertension and glaucoma, which comprises the step of ocularly administering a pharmacologically effective amount of a cannabimimetic pharmacological agent known to be selective for CB2 receptors to a patient in need of such treatment.

6. A method of treating ocular hypertension and glaucoma, which comprises the step of ocularly administering a pharmacologically effective amount of a compound of Claim 1, to a patient in need of such treatment.

7. A method of alleviating, treating or preventing, pulmonary disorders such as asthma, or chronic bronchitis; allergies and allergic reactions such as allergic rhinitis, contact dermatitis, or allergic conjunctivitis; inflamation such as arthritis or inflammatory

Q_2 is phenyl, naphthyl, quinolinyl, furanyl, thienyl, pyridinyl, anthracyl, benzothienyl, benzofuranyl or thieno[3,2-b]-pyridinyl, mono-, di- or trisubstituted with R^8;

HET is is a diradical of benzene, thiazole, thiophene, or furan, substituted with one or two R^9 groups;

Z is CO or a bond.

m is 0-6; and

n is 0,1, or 2.

2. The compounds of Claim 1, wherein,

R^1 is H, lower alkyl, or lower fluorinated alkyl;

R^{2-4} is independently H, lower alkyl, OR^1, halogen, or lower fluorinated alkyl;

R^7 is H, or lower alkyl; and

Q_1 is morpholine, piperazine, piperidine, or pyrrolidine.

3. The compounds of Claim 1, wherein

R^1 is lower alkyl;

R^{2-4} is independently is H, or OR^1;

R^7 is H;

Q_1 is morpholine;

m is 2; and

Z is a bond.

4. The compounds of Claim 1 which are:

2-[1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]ethanone;

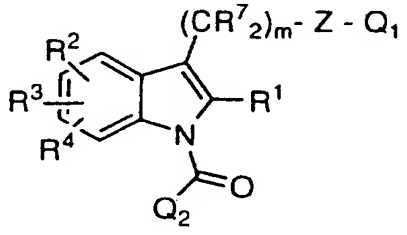
2-Methyl-3-(morpholin-4-yl)methyl-1-(1-naphthoyl)-1H-indole;

2-Methyl-1-(1-naphthoyl)-1H-indol-3-ylacetic acid, methyl ester;

1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-3-(morpholin-4-ylmethyl)-1*H*-indole;

WHAT IS CLAIMED IS:

1. A compound of the structural formula I:



I

pharmaceutically acceptable salts thereof, or diastereomers,or enantiomers or mixtures thereof,

wherein:

R^1 is	H, lower alkyl, aryl, benzyl, or lower fluorinated alkyl;
R^{2-4} is	independently, H, lower alkyl, lower fluorinated alkyl, halogen, NO_2, CN, $-(CR^7_2)m-OR^1$, $-(CR^7_2)m-S(O)_nR^6$, or $-(CR^7_2)m-R^6$;
R^5 is	H, lower alkyl, aryl, or benzyl;
R^6 is	lower alkyl, aryl, benzyl, or $N(R^5)_2$;
R^7 is	H, or lower alkyl;
R^8 is	R^7, lower fluorinated alkyl, halogen, OR^7, or lower alkyl thio;
R^9 is	R^7, lower fluorinated alkyl, halogen, OR^7, or lower alkyl thio;
Q_1 is	H, OR^7, CHO, CN, CO_2R^7, $C(O)SR^7$, $S(O)_nR^6$, HET or $N(R^7)_2$, wherein two R^7 groups may be joined to form a pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine ring and their quaternary methyl ammonium salts;

stirred 1h. The mixture was poored in saturated $NaHCO_3$ (25mL), extracted with EtOAc (2x50mL). The organic phase was washed with brine (50mL), dried over Na_2SO_4, filtered, concentrated and flash chromatographed (Silica gel ; EtOAc) to yield 503mg (99%) of the title compound.

^{1}NMR ($CDCl_3$, 400MHz) δ 2.12 (s, 3H), 2.52 (m, 6H), 2.79 (t, 2H), 3.74 (t, 4H), 3.82 (s, 3H), 6.71 (dd, 1H), 6.91 (d, 1H), 7.34 (m, 3H), 7.61 (dd, 1H).

Elemental analysis for $C_{23}H_{24}Cl_2N_2O_3$•HCl, calcd: C: 57.1, H: 5.21, N: 5.79; found: C: 57.18, H: 5.26, N: 5.70.

EXAMPLE 4

1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1H-indole

Step 1: 5-Methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1H-indole

To 5-methoxy-2-methyl-1H-indole (5.00g ; 31.0mmol) in 30 mL of dry THF at O°C was added dropwise MeMgBr (3.0M in Et_2O ; 11.4mL ; 34.2mmol). The solution was stirred 30 min at r.t. after which $ZnCl_2$ (0.5M in THF ; 64mL ; 32mmol) was added. The mixture was stirred at r.t., after 1h, N-(2-iodoethyl)morpholine (14.41g ; 51.5mmol) was added. The final mixture was stirred at r.t. overnight. The mixture was poored in saturated $NaHCO_3$ (100mL), extracted with EtOAc (2x100mL). The organic phase was washed with brine (100mL), dried over Na_2SO_4, filtered, concentrated and flash chromatographed (Silica gel ; EtOAc / Ace O to 10%) to yield 587mg (7%) of the title compound.

^{1}NMR ($CDCl_3$, 400MHz) δ 2.36 (s, 3H), 2.64 (bs, 6H), 2.92 (bs, 2H), 3.83 (bd, 4H), 3.85 (s, 3H), 6.76 (dd, 1H), 6.97 (d, 1H), 7.15 (d, 2H), 7.68 (bs, NH).

Step 2: 1-(2,3-Dichlorobenzoyl)-5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1H-indole

To 5-methoxy-2-methyl-3-(2-(morpholin-4-yl)ethyl)-1H-indole (311mg ; 1.13mmol) in 10 mL dry THF at -78°C was added HMPA (590µL ; 3.39mmol), then dropwise KHMDS (0.5M in Tol ; 2.5mL ; 1.25mmol). The solution was stirred 30 min at -22°C then cooled to -78°C after which 2,3-dichlorobenzoyl chloride (361mg ; 1.72mmol) was added. The final mixture was allowed to reach r.t. slowly then

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H), 3.64 (s, 3H), 3.68 (s, 2H), 7.05-7.13 (m, 2H), 7.22-7.26 (m, 1H), 7.49-7.52 (m, 1H) and 7.82 (s, 1H).

Step 2: 2-Methyl-1-(1-naphthoyl)-1H-indol-3-ylacetic acid, methyl ester

The compound of step 1 (1.13g; 5.56 mmol) in 6 mL of DMF was treated with NaH 80% (0.18g; 5.99 mmol) at 25° C. After 30 min a solution of 1-naphthoyl chloride in 5 mL of DMF was added dropwise The reaction mixture was left stirring for 16h and poured into cold water-EtOAc. The organic phase was washed with H_2O (2 X 15 mL) and brine, dried over Na_2SO_4 and the solvent removed. Chromatography on silica gel (eluted with 2% EtOAc in toluene) yielded 0.86g (43%) of the title compound.

^{1}H NMR ($CDCL_3$, 400 MHZ) Δ 2.20 (S, 3H), 3.67 (S, 3H), 7.0 (M, 1H), 7.10-7.26 (M, 3H), 7.45-7.60 (M, 5H), 7.95 (M, 1H) AND 8.07 (M, 3H).

High Resolution Mass Spectra results were: Formula ($C_{23}H_{19}NO_3+H^+$); Calculated (358.14415); Found (358.14432)

Step 2: 2-Methyl-3-(morpholin-4-yl)methyl-1-(1naphthoyl)-1H-indole

To the aldehyde (0.118g ; 0.38 mmol) from step 1 and morpholine hydrochloride (0.99g; 3.8 mmol) in 10 mL of MeOH was added $NaBH_3CN$ (0.057g; 0.91 mmol) and the mixture was left stirring for 16h at r.t. Another 60 mg of $NaBH_3CN$ was added and left stirring 8 h. The reaction was then poured into H_2O-EtOAc (20 mL- 50 mL) and saturated with NaCl. The organic extracts were washed with brine and dry over Na_2SO_4. The solvent was removed and the crude product purified by chromatography on silica gel (eluted with 10% → 30% EtOAc in toluene) to yield 0.99g (68%) of the title compound.

^1H NMR ($CDCl_3$, 400 MHz) δ 2.18 (s, 3H), 2.46 (m, 4H), 3.59 (s, 2H), 3.67 (m, 4H). 7.02 (t, 1H), 7.20 (m, 3H), 7.40-7.55 (m,2H) and 8.04 (d, 1H).

EXAMPLE 3

2-Methyl-1-(1-naphthoyl)-1H-indol-3-ylacetic acid, methyl ester

Step 1: 2-Methyl-1H-indol-3-ylacetic acid, methyl ester.

To 2-methyl indole (1.69 g; 12.9 mmol) in 10 mL of THF at 0° C was added MeMgBr 1.4M (12.9 mmol). After 30 min at 0° C. $ZnCl_2$ 1M (12.9 mL; 12.9 mmol) in THF was added and the reaction stirred for an other 30 min at r.t. Methyl bromoacetate (1.4 mL; 14.7 mmol) was added dropwise and left stirring for 48 h. The mixture was poured into aqueous $NaHCO_3$. extracted with EtOAc (3 X 25 mL) and the combined organic extracts were washed with brine. The solution was dried over Na_2SO_4 and the solvent removed. Chromatography on silica gel (eluted with 5% EtOAc in hexane) yielded 1.13g (43%) of the title compound.

chloride (0.33 mL; 2.61 mmol) was added and left stirring for 16 hr. It was then poured into cold water-EtOAc (50 mL). The organic phase was washed with H_2O (2 X 15 mL) and brine. The organic phase was dried over Na_2SO_4 and the solvent removed. Chromatography on silica gel (eluted with EtOAc) followed by a swish in CH_2Cl_2 (hot) - hexane afforded 0.462g (78%) of the title compound.

^1H NMR ($CDCl_3$, 400 MHz) δ 2.22 (s, 3H), 3.44 (m, 4H), 3.61 (s, 4H), 3.66 (s, 2H), 3.80 (s, 3H), 6.67-6.70 (dd, 1H), 6.96 (d, 1H), 7.10 (d, 1H), and 7.39-7.50 (m, 4H).

EXAMPLE 2

2-Methyl-3-(morpholin-4-yl)methyl-1-(1-naphthoyl)-1H-indole

Step 1: 3-Formyl-2-methyl-1-(1-naphthoyl)-1H-indole

To 3-formyl-2-methylindole (4.30g; 27.0 mmol) in 70 mL of DMF at r.t. was added NaH 80% (0.861 mg). After 30 min of stirring the solution was cooled to 0° C and a solution of 1-naphthoyl chloride (5.04g, 29.3 mmol) in 10 mL of DMF was added dropwise. The mixture was left stirring for 16h at r.t. and poured into cold water-EtOAc (100mL). The organic phase was washed with H_2O (2 X 25 mL) and brine. The organic phase was dried over Na_2SO_4 and the solvent removed. Chromatography on silica gel (eluted with 10% EtOAc in toluene) yielded 1.70g (20%) of the title compound.

^1H NMR ($CDCl_3$, 400 MHz) δ 2.64 (s, 3H), 6.95 (d, 1H), 7.04 (t, 1H), 7.10-7.30 (m, 1H), 7.51 (m, 1H), 7.59 (m, 3H), 7.96 (m, 1H), 8.11 (d, 1H) and 10.34 (s, 1H).

(milliliters), g (gram(s)), mg (milligram(s)), mol (moles), mmol (millimoles), eq. (equivalent(s)).

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

2-[1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]ethanone

Step 1: 2-[5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]-ethanone

To 5-methoxy-2-methyl-3-indoleacetic acid (0.665g; 3.03 mmol) in 6 mL of THF was added DCC (0.661g; 3.2 mmol). After 2 h of stirring, morpholine (1 mL; 11.4 mmol) was added and stirred for another 1 h. The reaction mixture was filtered and the solvent removed. Chromatography on silica gel (eluted with EtOAc) yielded 0.585g (64%) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H), 3.38 (m, 4H), 3.60 (m, 4H), 3.70 (s, 2H), 3.82 (s, 3H), 6.7 (m, 1H), 6.93 (s, 1H), 7.09 (d, 1H) and 7.97 (s, 1H).

Step 2: 2-[1-(2-Chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-1-[morpholin-4-yl]ethanone

To the amide (0.506g ; 1.75 mmol) from step 1 in 10 mL of THF and 0.9 mL of HMPA cooled to -78° C was added KHMDS 0.5 M (3.5 mL; 1.75 mmol) dropwise. The temperature was raised to -22° C for 30 min and brought back to -78° C. Then 2-chlorobenzoyl